Agomelatine is effective in reducing insomnia in abstinent alcohol-dependent patients

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Abstract: OBJECTIVES: Sleep disorders are a widespread, persistent problem among alcohol-dependent patients and have been implicated in an increased risk for alcohol relapse. The melatonin-agonist agomelatine has been shown to improve overall sleep quality without daytime sedation. METHODS: In an off-label therapeutic setting, 9 alcohol-dependent patients with chronic sleep disorders received nightly doses of between 25 and 50 mg of agomelatine. RESULTS: After 6 weeks of agomelatine treatment, the Pittsburgh Sleep Quality Index global score for all patients had decreased significantly from a mean (SD) of 13.1 (1.7) to 7.8 (1.7) ($t = 12.8$; $P = 0.00$). CONCLUSIONS: Agomelatine is a preparation that is not prone to abuse. The current pilot investigation shows that agomelatine might offer the prospect of becoming a valuable addition to the pharmacological repertoire for the treatment of alcohol-dependence-associated insomnia.

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Agomelatine Is Effective in Reducing Insomnia in Abstinent Alcohol-Dependent Patients

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Objectives: Sleep disorders are a widespread, persistent problem among alcohol-dependent patients and have been implicated in an increased risk for alcohol relapse. The melatonin-agonist agomelatine has been shown to improve overall sleep quality without daytime sedation.

Methods: In an off-label therapeutic setting, 9 alcohol-dependent patients with chronic sleep disorders received nightly doses of between 25 and 50 mg of agomelatine.

Results: After 6 weeks of agomelatine treatment, the Pittsburgh Sleep Quality Index global score for all patients had decreased significantly from a mean (SD) of 13.1 (1.7) to 7.8 (1.7) ($t = 12.8$; $P = 0.00$).

Conclusions: Agomelatine is a preparation that is not prone to abuse. The current pilot investigation shows that agomelatine might offer the prospect of becoming a valuable addition to the pharmacological repertoire for the treatment of alcohol-dependence–associated insomnia.

Key Words: alcohol dependence, insomnia, abstinence, agomelatine

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Among abstinent alcohol-dependent (AD) patients, sleep disorders are a widespread and persistent problem and have been associated with the risk for alcohol relapse.[1] Polysomnographic characteristics of AD patients include prolonged sleep latency and decreased sleep efficiency.[2] Abstinent AD patients also show abnormal evening melatonin profiles, including a peak delay of up to 90 minutes.[3] Although there is a comprehensive pharmacological repertoire for the treatment of insomnia, a history of AD significantly limits available options. Benzodiazepines are efficacious but should be considered as contraindicated because of their potential for abuse, overdose, and toxicity in combination with alcohol.[4] Antidepressant medications with sedative properties such as amitriptyline and doxepin have increasingly been used to treat insomnia[5] but are often lethal when taken as an overdose and/or in combination with alcohol and can induce sexual dysfunction. Mirtazapine also has sedative effects, but weight gain and/or impaired sexual function can lead to incompliance.[6] In addition, several anticonvulsant drugs (such as carbamazepine and gabapentin) have sedative effects and the therapeutic potential to aid sleep.[7] However, carbamazepine requires blood monitoring and is associated with hepatotoxicity, whereas gabapentin has been associated with an increased risk for suicide.[8] Other options include antipsychotic agents such as olanzapine that have known sedative effects, but again, associated sexual dysfunction and/or weight gain often result in incompliance.[9]

Agomelatine is a structural analog of melatonin and acts both as an agonist of the MT1 and MT2 receptors as well as an antagonist of 5-HT_{2C}. As such, agomelatine represents a new class of antidepressant and was approved for the treatment of major depression in 2009.[10] Because of its mechanism of action on melatonin receptors, agomelatine improves overall sleep quality without daytime sedation.[11,12] This effect is paralleled by changes in sleep electroencephalograms and indicates improvements in overall sleep architecture.[12] Furthermore, agomelatine was significantly less likely to cause sexual dysfunction in comparison with either paroxetine[13] or venlafaxine[14] and was not associated with weight gain or loss.[15] Together, these factors indicate that agomelatine is potentially a valuable new addition to current treatment options for insomnia in AD patients.

A well-known weakness of randomized controlled premarketing trials is the exclusion of patients with addiction disorders, resulting in a frequent lack of relevant naturalistic data on newly approved substances. The purposes of this retrospective case analysis were therefore to determine whether agomelatine was well tolerated and to examine the effect of agomelatine on sleep quality in abstinent AD patients with chronic sleep disorders. To our knowledge, this is the first naturalistic investigation of the relationship of agomelatine to sleep quality in AD.

METHODS

Participants

The sample consisted of 8 male and 1 female (outpatient) AD patients with persistent insomnia but without depression. All patients had no depression (mean HAMD-21 score, <10) or other psychiatric (except nicotine dependence) or neurological illnesses. The mean (SD) age of the participants was 47.2 (11.2) years, with a mean (SD) duration of AD of 20 (8.3) years. Before the current treatment, several patients were weaned off known sleep-promoting substances either because of their potential for abuse (benzodiazepines) or because they were not well tolerated, including impairment of sexual function and/or weight gain and/or daytime sedation (antidepressants, antipsychotics). Because most patients exhibited long-term AD, 7 of 9 patients received either disulfiram (1500 mg/wk) or naltrexone (50 mg/d) to prevent relapse.

Because agomelatine is potentially hepatotoxic, it was only prescribed in patients who fulfilled the following preconditions: (1) patients well known to our department with a proven history of reliability and timely and regular presentation, (2) patients who were comprehensively informed of the potential hepatotoxicity of agomelatine, particularly in combination with alcohol intake, and showed understanding of the necessity to rapidly reduce and cease agomelatine use in case of a relapse, (3) patients

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with no known liver diseases, and (4) patients who consented to repeated laboratory blood analyses before and during treatment.

Agomelatine Treatment

The study commenced with nightly oral doses of 25 mg in all patients. After 3 weeks, all patients were revisited and, in 6 of 9 patients, the dosage of agomelatine was increased to 50 mg/d because of its only partial effectiveness on sleep quality.

Assessment of Sleep Quality

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) before (T1) and after 6 weeks of treatment (T2) with agomelatine. The PSQI is a self-rated questionnaire that assesses sleep quality and disturbances. Nineteen individual items generate 7 "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The sum of scores for these 7 components yields 1 global score.

Laboratory Analysis

Before (T1) and during treatment with agomelatine (T2), all patients were monitored for serum levels of the liver enzymes γ-glutamyltransferase (GGT), alanine transaminase (ALT), and aspartate transaminase (AST).

Statistics

Statistical Package for the Social Sciences 16.0 (SPSS Inc, Chicago, Ill) was used for the statistical analyses. To compare PSQI scores and laboratory values before and after 6 weeks of treatment, 1 sample t test was performed. The level of significance was set at $\alpha < 0.05$. Mean data values are presented, together with standard errors of the mean.

RESULTS

Sleep Quality

All patients in our sample initially scored higher than 10 (mean [SD], 13.1 [1.7]) on the PSQI global score, indicating severe insomnia. After 6 weeks of agomelatine treatment, the PSQI global score for all patients had decreased significantly, to a mean (SD) of 7.8 (1.7) ($t = 12.8$; $P = 0.00$), (Table 1).

Laboratory Analyses

Hepatotoxicity of agomelatine, as appraised by serum levels of 3 liver enzymes, was not evident at the doses used in this study (Table 1).

Sexual Dysfunction and Weight Gain

Although we did not operationalize sexual functions, no decrease of sexual desire, erectile dysfunction, and/or orgasm disorders were reported by any of the participants after 6 weeks. Furthermore, no weight gain or other drug-related adverse effects were observed.

DISCUSSION

The present retrospective data suggest that agomelatine may improve the sleep quality of male AD patients with chronic AD-associated insomnia. As expected, adverse effects such as weight gain or sexual dysfunction were not observed during 6 weeks of treatment. Thus, agomelatine was well tolerated and all patients expressed their desire to continue the treatment under the conditions described previously.

However, post–marketing experience with agomelatine has demonstrated that one adverse effect is a possible increase in serum levels of liver enzymes. This led to a recommendation by the European Medicines Agency for liver function tests as a precautionary measure at the onset of treatment, then periodically at 6 and 12 weeks as well as 12 months, and, thereafter, when clinically indicated.[16] In addition, it should be noted that agomelatine is contraindicated in patients with hepatic impairment such as cirrhosis. Thus, in light of the possible liver toxicity of agomelatine in a population already vulnerable to liver disease per se, we strongly recommend that agomelatine be prescribed only to those AD patients who fulfill the criteria defined by us previously.

An important limitation in the present study is that most of the included patients have long-term alcoholism who are receiving treatment with disulfiram. Because disulfiram treatment triggers the formation of tryptophol, a compound that induces sleep,[17] the presence of this compound may influence the assessment of the sleep-inducing effect of agomelatine in AD. Furthermore, it is important to mention that, in general, retrospective case series with the absence of control groups provide only weak statistical evidence and can be prone to bias. On the other hand, case series can generate new hypotheses or possible

TABLE 1. Patients Characterized by Age and Sex

Age, y, Sex	Dosage, mg	PSQI (T1)	PSQI (T2)	GGT (T1)	GGT (T2)	AST (T1)	AST (T2)	ALT (T1)	ALT (T2)
49 (m)	25	12	8	38	19	22	19	41	19
57 (m)	50	14	7	21	18	18	23	13	17
58 (m)	50	11	5	18	39	17	20	10	14
45 (m)	25	13	8	23	15	60	27	42	22
43 (m)	50	11	7	30	27	23	27	28	24
65 (m)	50	16	11	26	24	33	41	34	33
43 (m)	50	12	9	30	28	31	30	29	21
33 (m)	50	15	8	31	33	37	36	55	47
32 (f)	25	14	9	58	23	28	24	28	13
Mean (SD)	—	13.1 (1.7)	7.8 (1.7)*	30.5 (3.9)	25.0 (3.2)*	29.8 (4.3)	27.5 (3.1)*	31.1 (4.7)	28.1 (7.0)*

Agomelatine dosage after 6 weeks.

Sleep quality and liver enzymes (U/L) before (T1) and after 6 weeks (T2).

*The statistical significance between the means of T1 and T2 ($P < 0.01$).

new treatment options that can be later tested under controlled conditions. In conclusion, agomelatine is a preparation that is not prone to abuse, shows a robust decrease in PSQI global score in AD patients, and now offers the prospect of becoming a valuable addition to the pharmacological repertoire for the treatment of AD-associated insomnia. To corroborate and extend our current data, we strongly recommend the further assessment in large controlled clinical trials.

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